BRIEF COMMUNICATION

Alcohol Consumption and the Risk of Bladder Cancer in the Framingham Heart Study

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The association between alcohol consumption and bladder cancer is controversial. We used data from 10 125 participants in the Framingham Heart Study to assess the association between total and beverage-specific alcohol consumption and the risk of bladder cancer. For each case of bladder cancer, up to five control subjects were selected and matched on major confounders using a risk set method. We used conditional logistic regression to assess the risk of bladder cancer according to categories of alcohol consumption. During a mean follow-up of 27.3 ± 10.1 years, there were 126 incident cases of bladder cancer. There was no statistically significant association between alcohol consumption and risk of bladder cancer (P_{trend} = .3). In beverage-specific analyses, beer consumption was associated with a reduced risk of bladder cancer (P_{trend} = .03), whereas wine (P_{trend} = .7) and spirit (P_{trend} = .2) consumption were not. Our data suggest that total and beverage-specific alcohol consumption are not associated with an increased risk of bladder cancer. [J Natl Cancer Inst 2004;96: 1397–1400]

Epidemiologic findings on the role of alcohol consumption in the development of bladder cancer have been inconsistent. Although most case–control studies found no association between total *(1–5)* and beverage-specific *(1,5)* alcohol consumption and bladder cancer, a meta-analysis *(6)* and the only prospective study *(7)* found suggestive evidence for an increased risk of bladder cancer in men who consume alcohol. Other European investigators have also reported a positive association between alcohol consumption and bladder cancer *(8,9)*. We sought to evaluate prospectively whether total and beverage-specific alcohol consumption are associated with an increased risk of bladder cancer among participants in the Framingham Heart Study.

The Framingham Heart Study is a population-based cohort study started in 1948 in Framingham, Massachusetts. The original cohort included 5209 participants. In 1971, children of the original cohort and their spouses were invited to participate in a prospective study called the Offspring Study. Detailed descriptions of the Framingham Heart Study have been published *(10,11)*. Informed consent was obtained from study participants, and the study protocol was approved by the Institutional Review Board of Boston Medical Center.

Incident cases of bladder cancer were identified by self-report at clinic visits during the Framingham Heart Study, by surveillance of hospital records at the local hospital in Framingham, and by search of the National Death Index *(12)*. For each suspected case of bladder cancer, histologic reports and the subject's medical chart were reviewed to determine the date of diagnosis and to classify the tumor according to the International Classification of Diseases in Oncology (topography code 188) *(13)*. Of the 133 confirmed cases of bladder cancer, seven case subjects were excluded because of preexisting bladder cancer (n = 3) or missing data on alcohol consumption (n = 4). The remaining 126 case subjects were included in the crude analysis; four cases with missing data on pack-years of cigarette smoking were excluded from the matched analyses.

Information on alcohol consumption has been collected repeatedly from both the original and offspring cohorts. At two early biennial examinations (examinations 2 and 7) of the original cohort, subjects were asked how many 2-oz cocktails, 8-oz glasses of beer, and 4-oz glasses of wine they consumed in a month. At examinations 12–15 and 17–23 of the original cohort, and at all examinations of the offspring cohort (i.e., every 4 years), subjects were asked how many 1.5-oz cocktails, 12-oz glasses (or cans) of beer, and 5-oz glasses of wine they consumed in a week. Details on alcohol assessment in the Framingham Heart Study have been previously described *(14)*.

Information on smoking was collected at each examination using standardized questions asked by the examining physician. Current nonsmokers were asked if they had ever smoked in the past; a positive answer was used to classify former smokers. To calculate pack-years of smoking, the average number of cigarettes smoked per day was divided by 20 and then multiplied by the number of years of cigarette smoking. Information on educational level was self-reported.

Because smoking is a strong risk factor for bladder cancer *(15)*, we used the risk set method *(16)* to control for confounding by smoking status, age, sex, and number of pack-years of smoking. For each case subject with bladder cancer, up to five control subjects were selected among individuals free of bladder cancer at the time the case subject was diagnosed and matched to the case subject by age (±2 years), sex, smoking status (never, former, and current), and number of pack-years of cigarette smoking (±4 pack-years) within each cohort. Each case subject was thus eligible to be a control during the interval preceding the bladder cancer occurrence of the index case subject.

Alcohol consumption was categorized as follows: 0, 0.1–6.0, 6.1–12.0, 12.1–24.0, 24.1–48.0, and greater than 48 grams per day. One "drink" contains

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approximately 12 grams of alcohol. We created indicator variables and used nondrinkers as the reference group. For each risk set, total alcohol consumption for each subject was computed as a weighted average of alcohol consumption from the baseline examination until the examination preceding the occurrence of bladder cancer in the case subject, and the number of pack-years of smoking for each subject was computed at the examination preceding the occurrence of bladder cancer in the index case subject.

We used a Cox proportional hazards model (conditional logistic regression) to estimate the adjusted relative risk (with 95% confidence intervals) of bladder cancer within alcohol categories, controlling for age, sex, cohort, smoking status, and pack-years of smoking. Adding educational level to the model did not change the results. For beverage-specific analyses, the model was adjusted for age, sex, cohort, smoking status, pack-years of smoking, and the consumption of other types of beverages. For example, the relative risks for categories of beer consumption were adjusted for wine and spirits intake. *P* values for trend were computed using the median alcohol value for each category as a continuous variable. Assumptions for the Cox proportional hazards model were tested (by including a product term consisting of time variable and alcohol exposure) and were met. All statistical tests were two-sided.

Of the 5209 participants from the original cohort, we excluded 205 subjects because of missing data on alcohol consumption (n = 202) or bladder cancer occurrence before the baseline examination (n = 3). Of the 5124 participants from the offspring cohort, we excluded three subjects because of missing data on alcohol consumption. Among 10 125 participants who were either case subjects with bladder cancer or free of bladder cancer and thus were eligible as potential controls, the mean age at baseline was 40.3 ± 10.4 years (range = 5–70 years). The baseline characteristics of the study population included in final analyses (n = 9821) are shown in Table 1. The mean follow up was 27.3 ± 10.1 years. Of the 122 case subjects included in the matched analyses, 118 had five control subjects, two had four control subjects, and two had three control subjects. Because the alcohol–bladder cancer association was similar between the original cohort (P_{trend} = .2) and the offspring cohort (P_{trend} = .3) and between men (P_{trend} = .5) and women (P_{trend} = .4), we present only combined data. There was no statistically significant interaction between alcohol consumption and smoking on the risk of bladder cancer (*P* = .5).

In a conditional logistic regression controlling for age, sex, cohort, and smoking variables, there was no evidence of an association between alcohol consumption and risk of bladder cancer (P_{trend} = .3; Table 2). Additional adjustment for educational level did not alter these findings (data not shown). There was a modest statistically nonsignificant increased risk of bladder cancer among subjects who consumed spirits (P_{trend} = .2) but no such increased risk among subjects who consumed wine. Consumption of beer was associated with a statistically significant reduced risk of bladder cancer (P_{trend} = .03; Table 2).

Contrary to our findings, a meta-analysis *(6)* and a prospective study *(7)* reported a 30%–60% increased risk of bladder cancer in men who consumed alcohol but not in women. Other investigators have suggested that alcohol dehydrogenase type 3 might influence the effects of alcohol on the risk of bladder cancer in that the odds of bladder cancer in moderate drinkers (i.e., those who consume two drinks per day) who were homozygous for the fast-oxidizing genotype ($\gamma_1\ \gamma_1$) was three times greater than that in moderate drinkers with other alcohol dehydrogenase type 3 genotypes *(9)*. We were unable to test for interaction with genetic factors in our analyses because we did not have data on those factors.

Limited prospective data are available on the effects of beverage-specific alcohol consumption on the risk of bladder cancer. Zeegers et al. *(7)* reported suggestive evidence (albeit not statistically significant) for an increased risk of bladder cancer with beer, wine, and spirits consumption in men. Our findings showed that individuals who consumed more than four drinks per week of spirits had a statistically nonsignificant slight increase in risk of bladder cancer; no increase was seen for wine consumption, and a slight decrease in risk was seen for beer consumption. The discrepancy between previous positive studies and our findings can be explained, in part, by several limitations across studies. First, our study has fewer heavy drinkers (i.e., consumption of more than four drinks per day) than other studies

Table 1. Baseline characteristics of the 9821 participants of the Framingham Heart Study included in the final analyses

Characteristic	Category of total alcohol consumption, g/day					
	0	0.1–6.0	6.1–12.0	12.1–24.0	24.1–48.0	>48.0
No. of subjects in category	2243	3052	1258	1380	1176	712
Mean alcohol consumption, g/day ± SD*	0 ± 0	3.8 ± 1.4	8.9 ± 1.7	17.1 ± 3.5	33.8 ± 6.8	74.8 ± 28.7
Male, %	30.1	34.9	52.9	58.5	70.9	83.2
Age, y ± SD	42.1 ± 11.9	39.2 ± 10.3	38.5 ± 9.7	39.0 ± 9.8	41.2 ± 9.4	42.5 ± 8.9
Offspring cohort, %	34.1	54.7	60.6	64.2	56.8	45.8
Years of education, %						
≤12	75.8	70.4	69.8	64.3	66.3	71.9
13–16	19.4	20.6	20.9	22.7	22.9	20.8
>16	4.9	9.0	9.2	13.0	10.8	7.3
Smoking status, %						
Never	59.1	42.8	30.7	27.2	19.7	13.7
Former	9.2	14.4	17.0	19.1	22.6	17.4
Current	31.7	42.8	52.3	53.8	57.7	69.0
No. of pack-years of cigarette smoking ± SD†	20.5 ± 18.8	18.7 ± 15.9	19.1 ± 14.9	21.0 ± 16.2	26.8 ± 18.0	34.9 ± 22.9

*For current drinkers. SD = standard deviation.

†For current smokers.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) of bladder cancer according to total and beverage-specific alcohol consumption in the Framingham Heart Study

Alcohol consumption groups	No. of case subjects/No. of control subjects*	HR (95% CI)†
Alcohol, g/day		
0	14/58	1.0 (referent)
0.1–6.0	43/192	0.9 (0.5 to 1.8)
6.1–12.0	21/96	0.9 (0.4 to 1.9)
12.1–24.0	14/96	0.6 (0.3 to 1.3)
24.1–48.0	22/96	0.9 (0.5 to 1.9)
>48.0	8/66	0.5 (0.2 to 1.2)
P_{trend}		.3
Beer, No. of drinks/wk		
0	48/188	1.0 (referent)
<1	20/107	0.6 (0.3 to 1.2)
1–4	23/104	0.7 (0.4 to 1.3)
>4	31/204	0.5 (0.2 to 0.8)
P_{trend}		.03
Wine, No. of drinks/wk		
0	49/216	1.0 (referent)
<1	42/201	0.9 (0.5 to 1.6)
1–4	17/113	0.6 (0.3 to 1.2)
>4	14/74	0.8 (0.4 to 1.7)
P_{trend}		.7
Spirits, No. of drinks/wk		
0	21/105	1.0 (referent)
<1	20/129	1.0 (0.5 to 2.0)
1–4	28/134	1.4 (0.7 to 2.9)
>4	53/236	1.6 (0.9 to 3.1)
P_{trend}		.2

*Matched on age (±2 years), sex, cohort, and smoking status (never, former, and current) and pack-years of cigarette smoking (±4 pack-years) for current smokers.

†Adjusted for age, sex, cohort, smoking status, and pack-years of cigarette smoking; for beverage-specific analyses, also controlled for other beverage types.

(4,7–9). Second, given that cigarette smoking is a strong risk factor for bladder cancer *(15)*, it is possible that residual confounding by smoking might partially explain some of the positive results *(8,9).* Because smoking is highly associated with alcohol consumption, it is often difficult to control correctly for the effects of smoking when assessing the effects of alcohol consumption. Simply adding smoking variables in the regression model—as has been the case in most studies—might not be sufficient to minimize confounding by smoking. In our study, we used a risk set method that matches each case of bladder cancer to control subjects on smoking status (never, former, or current smoker), pack-years of smoking (±4 years), and other major confounders such as age (±2 years). We have shown that results obtained from this technique are less likely to be biased by residual effects of smoking *(14).* For case–control studies with positive results, it could be difficult to eliminate selection and recall biases that are inherent in case–control study design. Further, because alcohol drinking patterns may change over time *(17)*, using a single measure of alcohol consumption (baseline value) might bias the results. To reduce the possibility of this bias, we used a weighted average of repeated measures of alcohol consumption over time.

Our study has several limitations, including the inability to separate life-long alcohol abstainers from former drinkers and the lack of data on fruit and vegetable consumption, which has been associated with a lower risk of bladder cancer *(18).* In addition, our findings are generalizable only to populations similar to the Framingham Heart Study participants who consume alcohol in moderate amounts (only 7% of our population consumed more than four drinks per day). Nevertheless, the use of stringent criteria to control confounding by smoking and other major risk factors, the use of average alcohol consumption up to the examination preceding the index case, and the wide age range of participants over two generations are strengths of our study.

In conclusion, our data show that total and beverage-specific alcohol consumption are not associated with an increased risk of bladder cancer. Although our findings are suggestive of a reduced risk of bladder cancer associated with beer consumption, future studies are needed to confirm these findings.

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NOTES

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